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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/352,466	07/13/1999	VIRGINIA C BROUDY	A-195CDDC	2305
21069	7590	01/29/2009		
AMGEN INC. MAIL STOP 28-2-C ONE AMGEN CENTER DRIVE THOUSAND OAKS, CA 91320-1799			EXAMINER BLANCHARD, DAVID J	
			ART UNIT	PAPER NUMBER
			1643	
			MAIL DATE	DELIVERY MODE
			01/29/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

09/352,466

Applicant(s)

BROUDY ET AL.

Examiner

David J. Blanchard

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 November 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 71-73 and 75-92 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 71-73 and 75-92 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 1-70 and 74 are cancelled.
Claims 71-72, 76-78, 82-84 and 87 have been amended.
2. Claims 71-73 and 75-92 are pending and under consideration.
3. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.
4. This Office Action contains New Grounds of rejections.

Objections/Rejections Withdrawn

5. The objection to the specification at pg. 1, line 26 because the terms "murine", "been" and "Cellular" are misspelled is withdrawn in view of the amendments to the specification filed 11/21/2008.
6. The objection to claim 83 as not ending in a period is withdrawn in view of the amendments to the claim
7. The rejection of claims 71-72 and 87-92 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation "leukemia therapeutic agent" in claims 71 and 87 and in the recitation of "solid tumor therapeutic agent" in claims 72 and 87 is withdrawn in view of the amendments to the claims.
8. The rejection of claim 81 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation "monoclonal antibody or fragment thereof comprises a murine hypervariable region and a human constant and framework region" is withdrawn upon further consideration of the claim.
9. The rejection of claim 82 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation "monoclonal antibody or fragment thereof comprises a murine hypervariable region and a human constant and framework region" is withdrawn in view of the amendments to claim 82
10. The rejection of claim 84 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation "monoclonal antibody or fragment thereof comprises a human monoclonal antibody" is withdrawn in view of the amendments to the claim.

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11. The rejection of claims 71-92 under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description is withdrawn in view of the amendments to the claims, i.e., deletion of the recitation "OCIM1 cells", and the cancellation of claim 74.

12. The rejection of claim 74 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as introducing new matter is withdrawn in view of the cancellation of the claim.

New Grounds of Rejections

It is noted that the following rejection was originally presented in the Office Action mailed 6/28/2006 and withdrawn in the previous Office Action mailed 5/23/2008 (see item no. 8 and advisory statement at pg. 3 of that Office Action). In view of the amendments to the claims, which no longer require the antibody bind OCIM1 cells, this rejection is being reapplied.

13. Claims 71-73 and 75-92 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating leukemia cells comprising administering a therapeutic agent conjugated to the monoclonal antibody produced from the hybridoma cell line ATCC No. HB 10716 (i.e., monoclonal antibody SR-1) or antigen-binding fragments thereof, wherein the monoclonal antibody or antigen-binding fragments thereof bind the human c-kit receptor and blocks binding of human stem cell factor, does not reasonably provide enablement for a method of treating just any cancer comprising administering to a patient a therapeutic agent conjugated to just any monoclonal antibody or fragment thereof that binds human c-kit and blocks binding of human stem cell factor. The specification does not enable any

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person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CAFC 1988).

Wands states on page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn to a method of inhibit the growth of leukemia cells and solid tumor cells in a patient comprising administering to a patient a therapeutic agent conjugated to a monoclonal antibody or fragment thereof or the monoclonal antibody produced from the hybridoma cell line having ATCC No. B10716, wherein the monoclonal antibody or fragment thereof binds human c-kit and blocks binding of stem cell factor to the receptor. Thus, the claims broadly encompass methods for inhibiting the growth of leukemic cells comprising administering a monoclonal antibody or fragment thereof that binds human c-kit and blocks binding of stem cell factor to the receptor as well as methods for inhibiting growth of solid tumor cells comprising administering a monoclonal antibody or fragment thereof or the monoclonal antibody produced from the hybridoma cell line having ATCC No. B10716, wherein the monoclonal antibody or fragment thereof binds human c-kit and blocks binding of stem cell factor to the receptor.

The specification teaches monoclonal antibody SR-1 produced by the hybridoma cell line ATCC No. HB 10716 that specifically binds the human c-kit receptor (see examples 2-4) and monoclonal antibody SR-1 blocks binding of radiolabelled human stem cell factor to the human erythroleukemia cell line, OCIM1, however, SR-1 does not block binding of radiolabelled art human stem cell factor to the murine MC/9 cell line (see example 5). The specification does not teach any other monoclonal antibody that

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binds the human c-kit receptor and blocks binding of stem cell factor to the receptor. There are no working examples of a monoclonal antibody other than monoclonal antibody SR-1 that binds the human c-kit receptor and blocks binding of stem cell factor. There are now working examples of an *in vivo* cancer model system wherein administration of monoclonal antibody SR-1 inhibits binding of stem cell factor to the receptor and neutralizes the biological effect of stem cell factor, i.e., neutralizes the growth rate of cancerous cells in the subject. Therefore, the teachings in the specification are extremely narrow relative to the broad scope of the claims at issue. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 19 24 (CCPA 1970).

The state of the prior art is such that the “role of c-kit in cancer is somewhat ambiguous” pg. 69, 1st col. of Lennartsson et al, Current Cancer Drug Targets, 6:65-75, 2006, cited on PTO-892 mailed 6/28/06. Lennartsson et al also teach that while a number of cancers are associated with the activation of c-kit, there are also a number of tumor forms, such as breast cancer, thyroid carcinomas and melanomas in which progression into a malignant phenotype occurs concomitantly with a loss of c-kit expression (pg. 69). *According to applicants’ specification, the prior art has not been able to obtain a monoclonal antibody to the c-kit receptor with any expectation that such a monoclonal antibody would possess the ability to block the binding of the c-kit ligand, stem cell factor (see specification at pg. 2).* Further, the art of Ashman et al (J. Cell Physiol. 158:545-554, 1994) submitted by applicant as Exhibit A in the reply filed 12/29/05 teach three different monoclonal antibodies to the human c-kit receptor. Monoclonal antibody SR-1 potentially blocked the binding of stem cell factor to the human c-kit receptor on HEL-DR and MO7e cells, whereas monoclonal antibodies YB5.B8 and 17F11 had minimal effects on ligand binding. Further, SR-1 potently inhibited the proliferative response to stem cell factor, while 17F11 weakly inhibited and YB5.B8 had negligible effect. The specification teaches that monoclonal antibody SR-1 was produced by immunization of mice with cells of the OCIM1 line, however, immunization of mice with OCIM1 cells will not necessarily or predictably reproduce a monoclonal antibody possessing the properties of monoclonal antibody SR-1. The

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specification does not define or characterize the epitope of human c-kit to which the SR-1 antibody binds. There is insufficient guidance and direction to assist the skilled artisan in producing a monoclonal antibody other than monoclonal antibody SR-1 that binds the human c-kit receptor and blocks binding of human stem cell factor to the receptor for the treatment of cancer. There is no direction or guidance provided by applicant to assist the skilled artisan in producing a monoclonal antibody that binds a human stem cell factor receptor and blocks the binding of stem cell factor to the receptor. The skilled artisan could not predictably extrapolate the teachings in the specification, limited to the production of monoclonal antibody SR-1 specific for the human c-kit receptor to the production of just any monoclonal antibody that binds just any human stem cell factor that blocks the binding of stem cell factor to the receptor for the treatment of just any cancer. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. *In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971). However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work.

Further, as stated in the office action mailed 2/28/2005 one cannot extrapolate the teaching of the specification to the claims because Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39, cited on PTO-892 mailed 2/28/05) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly

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possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (bridging paragraph pp. 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). In addition, Jain (Sci. Am 271:58, 1994, cited on PTO-892 mailed 2/28/05) discloses the art known barriers to the delivery of drugs into solid tumors. Impediments to drug delivery include (1) Nonuniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1); (4) Convection is a necessary mechanism by which larger therapeutics molecules such as antibodies, reach target cells which are not directly fed by the vasculature. Convection is not observed in large tumors (defined as more than centimeter in diameter, page 62 col. 1) and convection is necessary for adequate drug delivery of molecules having a molecular weight of more than 5000 (page 61, col. 1 through page 63, col. 3) and (4) Molecules as large as antibodies (i.e., MW=150,000) would require several months to reach a uniform concentration in a tumor that measures 1 centimeter in radius (page 63, col. 2). The present disclosure provides no objective evidence or working examples for treating cancer in a subject (i.e., *in vivo* animal model) to lend one of ordinary skill in the art a reasonable expectation of success. Lack of working examples is given added weight in cases involving an unpredictable and undeveloped art such as the treatment of cancer with human c-kit specific antibodies as discussed above.

In view of the lack of the predictability of the art to which the invention pertains as evidenced by Lennartsson et al, Ashman et al, Curi and Jain (all of record), the lack of guidance and direction provided by applicant, and the absence of working examples, undue experimentation would be required to practice the claimed method of inhibiting the growth of just any cancer (i.e., solid tumor) in a patient comprising a monoclonal

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antibody conjugated to a therapeutic agent wherein the monoclonal antibody binds human c-kit and blocks binding of human stem cell factor with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed cancer therapy and absent working examples providing evidence which is reasonably predictive that the claimed monoclonal antibodies bind human c-kit and block the binding of stem cell factor thereby decreasing the growth rate of just any cancer in a patient, commensurate in scope with the claimed invention.

14. No claim is allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

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The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/
Primary Examiner, A.U. 1643